Ensuring Good Manufacturing Practices for Cell & Gene Therapies

A 10-Point CQV Checklist

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Expanding and Adapting: The State of the U.S. Cell & Gene Therapy Market

With the boom in demand and production of cell and gene therapies (CGT) over the last decade, biopharma manufacturers are continually adapting to capitalize on market trends and address necessary equipment and facility upgrades.

In the U.S., regional CGT manufacturing has materialized a diverse set of production capabilities in life sciences clusters throughout the country, with capacity limitations and the need for specialized, high-tech genetic engineering systems dictating facility expansions and repurposing.

Manufacturers that can strike the right balance of technology, personnel, and partnerships can overcome the CGT market limitations and growing pains to establish and maintain good manufacturing practices and capitalize on the market trajectory.

Cell & Gene Therapy Market Snapshot	
Global market size 2020:	**$4.39B[1]**
Expected global market size 2025:	**$15.48B[1]**
Expected global market size 2030:	**$34.31B[1]**
Global clinical trials involving gene therapies:	**4,769***
U.S. clinical trials involving gene therapies:	**2,433***

*Based on a ClinicalTrials.gov database search of all recruitment statuses and study phases at time of writing.

Growing Clusters and Emerging Pods

While perennial top-ranked life sciences clusters have been extremely beneficial to the industry in terms of concentrating skilled professionals, training programs, collaborators, and investors, this regionalization has put a squeeze on critical resources, such as real estate, to a point where smaller companies can't afford to compete for space in these sought-after locales.

Over the past several years, the industry has witnessed the continued movement of life sciences companies setting out to find new lands of opportunity. Typically concentrating near universities and research institutions, these pioneer companies are responsible for helping cities climb the list of top life sciences clusters and putting new cities on the map.

Figure 1. The top 13 U.S. life sciences clusters and the top 10 emerging life sciences clusters according to CBRE Research, Q3 2020.[2]

While many companies prefer to purchase existing buildings to speed time to market, the supply of 100,000+ square-foot spaces is dwindling, especially in these hyper-competitive markets. Manufacturers looking to expand operations are forced to pursue both new construction and retrofitting options simultaneously, weighing the costs and timelines of each.

Once an existing building or new site is acquired, the timeline becomes a relentless focus.

One aspect that can help streamline these massive project schedules and get to operational readiness on time is integrating all commissioning, qualification, and validation (CQV) activities from the start.

A 10-Point Checklist for Cell & Gene Therapy Facility Commissioning, Qualification, and Validation

CGT facilities present unique CQV challenges specific to the production of these novel therapies.

There are several steps that biopharmaceutical companies should take to keep greenfield and brownfield CGT facility projects ahead of schedule and under budget — all while demonstrating good manufacturing processes.

1. CQV the Right Equipment

The equipment used in the manufacturing process for CGT is a critical component that requires much planning.

- Does the equipment you own or intend to purchase meet all of your process requirements?
- For new equipment, what is the procurement lead time?
- How will procurement timelines factor into the overall project schedule?
- Is there a contingency plan if the equipment is delayed or damaged?

If you use equipment for automated processes, you should have fail-safes built into the design of the hardware and software. Seek a partner that can help you through the early basis of design stages to ensure you meet manufacturing timing and requirements as well as achieve regulatory compliance.

2. Check Procurement Timelines for SUS

Production of CGT also requires the procurement of single-use systems (SUS) that must meet requirements for sterility, stability, physical integrity, and strength. Still, it can be challenging to find a reliable supplier, especially with supply chain issues stemming from the COVID-19 pandemic.

It's crucial to align the procurement of specialized equipment, including SUS, around timelines for construction, utility installation, and the facility plan. Allow for additional time to find a supplier for customized manufacturing equipment.

3. Apply Custom Off-the-Shelf Approaches

The use of custom off-the-shelf (COTS) approaches, especially for CGT, has significantly increased over the last decade. Innovative COTS qualification strategies can produce significant cost savings and help you reach your capital project milestones months ahead of schedule.

4. Conduct a Vendor Site Audit

Vetting and auditing each vendor that will contribute to the build-out can help you identify and avoid potential quality issues before they impact your timeline.

When it comes time to conduct a vendor site audit for quality, data integrity, and security, establish a single point of contact to avoid miscommunication. Your vendors' quality systems need to be rigorous and their data security measures need to pass your audit with flying colors and meet the FDA's requirements for Computer System Validation (CSV) guidelines and 21 CFR Part 11.

5. Establish or Refine a Best-Practice QRM Process

Quality risk management (QRM) should include repeatable processes designed to coordinate, facilitate, and improve decision-making related to risk. Any QRM planning process should involve:

- Defining the problem and risk question, including pertinent assumptions identifying if the risk might happen
- Assembling background information and data on the potential hazard, harm, or human health impact relevant to the risk assessment
- Identifying a leader or risk owner and if additional resources are needed
- Specifying a timeline, deliverables, and appropriate level of decision-making for the risk management process

6. Consider Continuous Manufacturing

Batch processing, while trusted and methodical, is time-consuming. With every step introduced into the process, a new door opens for human error, contamination, and delays. One study estimates that inefficient batch processes cost the pharmaceutical industry upwards of $50 billion annually due to contamination, losses, and recalls.[3]

The President's Council of Advisors on Science and Technology also reported that a 40–50% reduction in manufacturing costs may be achievable with continuous manufacturing[4], which could be instrumental in making drugs more affordable to patients and increasing the availability of critical pharmaceuticals, both major topics of conversation in the U.S.

In addition to higher product yields and consistency in product quality, continuous bioprocessing can also reduce the required physical manufacturing footprint by as much as 40–90%[5], which is welcome news to those struggling to find suitable real estate.

7. Use a Flexible Approach

Facilities, technologies, and equipment used for CGT production are still evolving, and there is no one-size-fits-all method for designing them. It's essential to maintain a flexible approach that can accommodate your facility's future needs, which will reduce downtime when expansions or changes arise.

When engineering and commissioning a CGT facility, consider flexible manufacturing suites and single-use systems that can be reconfigured to accommodate changing production needs and small-batch processing.

8. Invest in Isolators

Your production process needs to be protected from contamination by pathogenic microorganisms. Isolators offer an enclosed, gas-tight area where aseptic manufacturing processes can be safely carried out within an HVAC cleanroom.

The proper custom isolator setup can reduce the use of protective safety suits, airlocks, and energy, all while keeping personnel safe from potentially harmful substances.

Qualification of isolator systems involves validating air velocity, airflow, and HEPA filter integrity, as well as monitoring pressure, particulates, microbes, temperature, humidity, and more.

Robotic or "gloveless" isolators offer additional benefits, such as the decreased risk of human intervention leading to error or contamination and greater flexibility for small-batch production.

9. Shorten Validation Review and Approval Cycles

Strategically combining documents to reduce the number of review, approval, and release cycles can shorten processes while still following GMP requirements. For example, consider these time-saving tips:

- Forgo formal Site Acceptance Testing (SAT) since all critical systems will be independently qualified
- Combine IOV and IOQ instead of IV then OV and IQ then OQ sequentially
- Add final reports as checklists for IOV and IOQ

Developing a library of modular templates will further streamline your documentation efforts.

10. Follow All Industry Guidelines

In addition to following established industry regulations, stay up to date on the evolving guidance related to CGT. Consider these documents and resources for CGT good manufacturing practices:

FDA 21 CFR Part 210, 211, 606, 630, and 1271 (Revised April 1, 2020)

- **21 CFR Part 210:** Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General
- **21 CFR Part 211:** Current Good Manufacturing Practice for Finished Pharmaceuticals
- **21 CFR Part 606:** Current Good Manufacturing Practice for Blood and Blood Components
- **21 CFR Part 630:** Requirements for Blood and Blood Components Intended for Transfusion or for Further Manufacturing Use
- **21 CFR Part 1271:** Human Cells, Tissues, and Cellular and Tissue-Based Products *(For applicable cell and tissue products, Part 1271 applies before the more general requirements in Parts 210 and 211)*

CBER Cellular & Gene Therapy Guidance
The Center for Biologics Evaluation and Research (CBER) has published several guidance documents in the last few years pertaining to investigational new drug applications (INDs); chemistry, manufacturing, and control (CMC) information; study design; reporting; and more.

These drafts are all available at:
https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/cellular-gene-therapy-guidances

EudraLex Guidelines on Good Manufacturing Practices for Advanced Therapy Medicinal Products (ATMP)
CGT is widely known as ATMP throughout Europe. ATMPs fall into three categories: gene therapy medicines, somatic-cell therapy medicines, and tissue-engineered medicines.

Any U.S.-based manufacturer intending to sell product in the EU market must comply with these guidelines.

ISPE GAMP 5
Demonstrate efficient use of ISPE GAMP 5 guidelines to achieve GMP compliance for all computerized systems used in CGT manufacturing processes.

A CGT CQV Case Study: Paragon/Catalent

When Paragon Bioservices (now Catalent Cell & Gene Therapy) began construction on a flexible contract biomanufacturing facility for gene therapies, vaccines, and advanced biologics near the Baltimore/Washington International Airport, they soon realized a need for construction coordination support and CQV program development to achieve key milestone dates.

Project controls, resource loading, schedule integration, change management, and budget controls were integrated into the overall project schedule.

As a result, Paragon Bioservices:

- **Completed facility start-up on time and under budget**
- **Achieved milestones prior to regulatory inspections**
- **Implemented a system to reduce regulatory burdens for future changes and repairs**

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About ICQ

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ICQ's biopharma focus, 75+ years of combined industry leadership, and deep bench strength of qualified CQV professionals ensure strict adherence to industry regulations, internal quality standards, and mission-critical project schedules and budgets.

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